REMARKS

Claim 28 has been amended in accordance with the kind suggestion of the Examiner to clarify that the nucleic acid molecule being claimed is not as it exists in its native state which, of course, would clearly be nonstatutory. No new matter has been added and entry of the amendment is respectfully requested.

Applicants appreciate the clarification of issues in the present Office action; both the supplementary written rejections and the discussion at the interview were most helpful in this regard. Applicants also appreciate the acknowledgement of the declaration filed 11 June 2001. The present claims are being pursued in the context of a Continuing Prosecution Application. Applicants note that claim 34 has not been considered.

The Invention

Applicants have, for the first time, obtained a nucleotide sequence which is of sufficient length to provide the art with a functional T-type calcium channel α_1 subunit. As noted in the specification, the α_1 subunit of T-type channels is functional by itself. Although the amino acid sequence encoded by SEQ. ID. NO: 18 does not represent the entire native α_1 subunit, this does not mean a functional channel has not been disclosed. As verified by the declaration of Dr. Terrance Snutch, already of record, the recovered sequence is sufficiently complete that the ordinarily skilled artisan can extend the protein encoded by this sequence into a functional α_1 subunit without any experimentation at all. Thus, the invention does place in the art a functional α_1 subunit of a T-type calcium ion channel for the first time. In addition, because of this work, by employing conditions of appropriate stringency, it is possible to obtain additional variants of this α_1 subunit characteristic of T-type calcium channels without undue experimentation. In

effect, therefore, applicants have placed in the art the universe of functional α_1 subunits of T-type calcium ion channels.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

There are two aspects of this rejection. One relates to the discussion above - because the sequence recited in the claims, SEQ. ID. NO: 18 is not a complete amino acid sequence of the naturally occurring channel, the Office concludes that the claims cannot be directed to a functional calcium channel α_1 subunit. The second aspect has to do with indefiniteness because of specifying "conditions of medium hybridization stringency." These points will be dealt with in turn.

As to the first point, applicants believe that the Office has provided no rationale to question the veracity or conclusions drawn in the declaration of Dr. Snutch. As Dr. Snutch explained in his declaration, because the characteristics of α_1 subunits of calcium ion channels in general are understood in the art, the information provided by SEQ. ID. NO: 18 is sufficient to provide a subunit which is functional in transporting calcium ions. In accordance with the Examiner's kind suggestion, applicants now indicate the sections of Dr. Snutch's declaration, which was filed accompanying a previous response, to which particular attention should be paid.

First, in paragraph 2 of the declaration, Dr. Snutch outlines the known characteristics which are common to calcium ion channels in general. He points out that each has four homologous domains separated by six transmembrane regions. He points out that each has a pore region which contains specific amino acid residues that are responsible for ion selectivity. The sequence retrieved in SEQ. ID. NO: 18, because of the nature of the amino acids in the three homologous regions encoded by this clone, allows the artisan to conclude that this is a calcium ion channel.

In addition, in paragraph 3, Dr. Snutch points out that the sequence encoded as SEQ. ID. NO: 18 has characteristics which, by comparing it to the known sequences of P/Q, N, and R channels, permit the conclusion that a T-type channel is encoded. This is because it was understood in the art that an additional type of calcium channel identified by its functional characteristics existed, but no clone exhibiting these characteristics had yet been found. Thus, SEQ. ID. NO: 18 represents the missing member of the calcium ion channel family. Paragraph 4 expands on this as well.

Paragraphs 5 and 6 provide additional evidence that SEQ. ID. NO: 18 encodes with α_1 subunit of T-type calcium channels. This is established through comparison with amino acid sequences of the previously cloned channels.

Of particular importance is paragraph 8. Because a start codon is present in the nucleotide sequence encoding SEQ. ID. NO: 18, the N-terminus is established. Again, by comparison to known calcium ion channels, it is evident that the complete homologous structural domains I, II and III and up to the S1 transmembrane fragment of domain IV are included in this clone. Because of the symmetry required and known from the studies of other calcium ion channels, it is possible to deduce an amino acid sequence for the missing domain IV by analogy to the domain III that is present.

Thus, Dr. Snutch's declaration establishes that given the information contained in SEQ. ID. NO: 18, a functional α_1 subunit is inherently disclosed by virtue of the fact that the sequence of domain III contained in the clone is a paradigm for the missing domain IV; one of ordinary skill would understand from the information in SEQ. ID. NO: 18 the entire sequence of a functional α_1 subunit. As there is no reason provided to doubt the sworn statements of Dr. Snutch, respectfully, the Office is obliged to acknowledge that the minor portions of the amino acid sequence not contained in SEQ. ID. NO: 18 are inherently disclosed by the

information contained in SEQ. ID. NO: 18. Thus, a written description which demonstrates that applicants were in possession of a functional α_1 subunit of a T-type receptor is contained in the application, and this aspect of the rejection should be withdrawn.

As to hybridization conditions of "medium stringency," applicants believe that this is sufficiently precise to define the metes and bounds of the invention. It will be recalled that a similar concern was raised with regard to claims which characterized amino acid sequences or nucleotide sequence in terms of percentage homology or percentage identity unless the algorithm by which this is calculated was specified. The concern was that, depending on the algorithm, a different answer might be obtained and therefore the exact metes and bounds of the claimed subject matter was uncertain.

Realizing that this was inconsistent with the understanding in the art, the Office elected to treat such limitations as having their broadest possible interpretation, thus permitting the widest range of prior art to be considered. Consistent with this approach, applicants believe that the claims should be interpreted to include sequences which hybridize under conditions corresponding to the lower limits of stringency as set forth in Dr. Snutch's declaration. As the hybridization is determined by the stringency of the final wash, the lowest stringency conditions within the range of medium stringency would be 0.1% SDS, 2 x SSPE, and 55°C. (See page 2 of Dr. Snutch's declaration submitted 10 October 2000.)

While applicants understand that without specifying the final wash conditions, a bright line has not been drawn in the sand as to the metes and bounds of the claims, it is believed that a description of "medium stringency" is sufficiently precise that one of ordinary skill could deduce the metes and bounds of the claim. It is also noted that no official notice was provided any applicants that specific hybridization conditions would be required at the time the present application was filed. This *ex post facto* policy is believed unfair to applicants who believe they

were entitled to rely on the practice of an Office which at one time, at least, permitted issuance of claims where hybridization to a known sequence was permitted as a limitation of the claim without specifying any limitations on the hybridization conditions at all.

In view of the foregoing, it is believed that the rejections of claims 28-33 may be withdrawn. It is noted that the aspect of the rejection related to the stringency conditions does not apply to claims 29 and 30.

The Rejection Under 35 U.S.C. §§ 101/112, first paragraph

First, applicants appreciate the Examiner's accurate summary of applicants' arguments.

In response to the statements made by the Office on page 8 of the Office action, applicants note that they are not claiming a nucleotide sequence which encodes a protein whose metes and bounds are that of SEQ. ID. NO: 18, but merely a nucleotide sequence that encodes a protein that includes the amino acid sequence represented by SEQ. ID. NO: 18. Thus, it is only a requirement that the codons for the amino acid sequence represented by SEQ. ID. NO: 18 be contained in the nucleic acid molecule which is the subject of the claim, and does not imply that this sequence cannot be extended if necessary in order to obtain a coding sequence for a functional protein. That is what has been done here. The claims are specifically directed to a nucleotide sequence encoding a functional T-type low voltage activated calcium channel α_1 subunit.

At the risk of being redundant, applicants restate that the claims are not directed, as the Office appears to interpret them, to a nucleotide sequence encoding a protein which is only a portion of the calcium ion channel. Rather, as conclusively shown by Dr. Snutch's declaration, the description of a nucleotide sequence which encodes a functional α_1 subunit of a T-type

channel is inherent in the disclosed SEQ. ID. NO: 18, and it is the extended form of SEQ. ID NO. 18 that the claims are directed to.

The Office does not contradict, as it cannot, applicants' statement that α_1 subunits are functional calcium channels in and of themselves. There is no necessity to clone any other channels in order to provide functionality. It is not seen that there is any statement anywhere which states such a necessity other than that hypothesized by the Office itself. The position of the Office that it would be necessary to obtain and clone various β subunits, as stated on page 8 of the Office action, is simply not true. Again, the Office itself recognizes that β subunits merely modulate the calcium ion channel activity of α_1 subunits; they are by no means required for the α_1 subunit to be useful and to carry out the function of a calcium ion channel.

The Office then addresses the issue of whether it is useful to screen libraries for compounds which agonize or antagonize the T-type calcium channel.

Applicants are genuinely puzzled by the statement that the functionality of the T-type calcium channel has not been disclosed. The Office itself concedes that applicants have disclosed a substantial number of conditions that are affected by calcium ion channels, and certainly the function of the channel is known - it is responsible for calcium ion transport into cells. The specification on page 9, at lines 7-12, clearly lists specific conditions which are affected by abnormal functioning of calcium ion channels. In addition to Dr. Snutch's declaration already of record (paragraphs 10-11) a declaration filed in the daughter application herein demonstrates, citing peer-reviewed publications, that conditions associated with T-type channel dysfunction are well known in the art. A copy of that declaration is included as Exhibit B.

In summary, it is simply not true that the function of the T-type calcium channel has not been disclosed.

Further, the Office supplies no basis for its statement that there are no known agonists for the claimed calcium channel and its conclusion that, therefore, the effective antagonist cannot be determined. Whether this is true is irrelevant, since one of the uses for the calcium ion channel subunits of the invention is to find such agonists. It seems equally irrelevant that the applicants have not identified any of these agonists or antagonists. Is the Office stating that such agonists and antagonists are presumed not to exist and therefore the screening described by the applicants would inherently be unsuccessful?

The general position taken in the bridging paragraph, on pages 9-10, is not consistent with legal requirements for patentability. Applicants have described and called the attention of the Office to specific conditions which are associated with malfunctioning calcium ion channels of the T-type. Applicants are not required to show an inevitable nexus between a particular antagonist or agonist and treatment of a condition that will play out through all the vagaries of tests in the clinic (*In re Brana*, 34 USPQ2d 1437 (Fed. Cir. 1995)).

The further argument on page 10 that not all lines have been drawn, not all t's have been crossed and not all i's have been dotted is inconsistent with the standards required for patentability.

In this regard, applicants wish to call the attention of the Office to U.S. patent 6,358,706 which claims a nucleic acid that contains a nucleotide sequence encoding an α_{1G} subunit of a T-type receptor. This patent, issued on an application filed 26 October 1999, appears to acknowledge the utility described herein for the claimed subunits. In the course of the interview regarding this application which was acknowledged above, the Examiner stated that in his view, utility for the T-type receptor was shown by the '706 patent because the clone obtained, when expressed in Xenopus oocytes was demonstrated to bind to mibefradil. No explanation is provided in the '706 patent as to what mibefradil might be. If it is simply a compound used to

classify calcium ion channels, it is unclear to applicants how this advances the notion that calcium ion channels of the type to which it binds are associated with any particular disease or condition. If mibefradil is a pharmaceutical, the same statement applies. There is no necessary causal relationship between any effect mibefradil may have on a specific condition with its ability to bind a calcium ion channel; this may simply constitute a side effect of no relevance whatever in regard to the role of the calcium ion channel in the condition. Certainly the '706 patent draws no such conclusion. The '706 patent, rather, lists a multiplicity of conditions in column 17, beginning at line 17, and continuing to column 18, line 5, which are associated with malfunction of the T-type channel.

The Examiner's implied criticism during the interview, that listing a multiplicity of conditions defeats the credibility of the asserted utility seems inconsistent with the disclosure in the '706 patent.

A similar situation occurs with respect to U.S. patent 6,309,858, which also claims nucleotide sequence encoding an α_1 subunit of a T-type channel. The situation with respect to the nexus between calcium ion channel irregularities and abnormal conditions is set forth in roughly the same fashion as that herein. That text simply says at column 9, lines 47-54, that the α_1 subunits which have been cloned by the applicants in that case are used to screen compounds useful in the treatment or prevention of "pain" of various types, and provides no evidence of the nexus between the cloned nucleic acid and any of these conditions.

If, indeed, the refusal to acknowledge that the claimed nucleic acid of the applicants has utility for screening compounds for this condition is a reflection of Office policy, it appears that that policy has not been applied to either the '706 or the '858 patents.

The extensive discussion of *Brenner v. Manson* is appreciated, but the facts are entirely different. The claims in *Brenner* were directed to a method to prepare a compound for which no

utility was disclosed, except to find out what the compound was good for. Applicants know what the T-type channel is good for - it is not to figure out what its own function is, but rather to identify agonists and antagonists, which use has been described, just as it was in the '706 and '858 patents.

The Office appears to misunderstand the point made by applicants that all T-type channels are sufficiently similar that an agonist for one would be an agonist for all and an antagonist for one would be an antagonist for all. Applicants do not argue that all T-type calcium ion channels have the same connection to disease states. On the contrary, applicants are saying that T-type channels bind to similar ligands regardless of the particular connection of a subset of such channels with a particular condition. As a result, a positive result for a T-type channel which occurs in neurons is indicative of a positive results for a T-type channel which occurs elsewhere in the subject's tissues.

The remaining arguments made by the Office on pages 13-14 appear redundant and it is believed that these have already been addressed above.

With regard to the statements on pages 16-18 related to *Ex parte Maizel*, respectfully, the specific points raised therein have been responded to above. The present claims have limitations directed to structural features. Even the Office concedes that medium stringency conditions represent a narrow range of conditions and thus clearly define an outer limit of sequences that can be included. This is vastly, vastly different from *Ex parte Maizel* where there are no structural limitations whatsoever imposed on the claimed subject matter.

The Rejection Based On Written Description

Again, applicants appreciate that the Office has accurately summarized their arguments. In response to the comments on pages 20-21, it has been explained above that (1) a sufficient

description has been provided to place a functional α_1 subunit of a T-type channel in the possession of the art and (2) that the structural definition is sufficiently precise for the metes and bounds of the invention to be evaluated. The support for applicants position is found in sworn testimony by Dr. Snutch.

The Rejection Under 35 U.S.C. § 101

The Office objects that claims 28-30 coincidentally read on naturally occurring DNA molecules which occur in the chromosome. This is, of course, not the intent. Applicants appreciate the suggestion that the word "isolated" be added to claim 28, and this has been added by amendment. Accordingly, this basis for rejection may be withdrawn.

CONCLUSION

There appear to be just three outstanding substantive issues. First, have applicants placed into the possession of the art an adequately described functional α_1 subunit of a T-type calcium ion channel? Based on Dr. Snutch's declaration, which has not been controverted, the clear answer to this question is yes. Second, is the nexus between abnormality of T-type channel activity and specific disease conditions sufficiently well-established that it is useful to discover agonists and antagonists of these channels? Again, the answer to this question is clearly yes. Two patents have already issued on this basis and the function of such channels is well known in the art and is described in the specification. Third, does specification of "medium stringency" provide a sufficiently defined boundary to comply with the statute? Again, the answer is yes, since a reasonable outer limit can be set as by analogy to the issue faced earlier by the Office with regard to percent homology. Accordingly, applicants believe that claims 28-33 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000700.

Respectfully submitted,

Dated: April 10, 2002

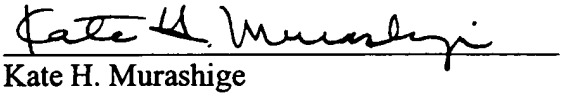
By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

28. (Twice amended) An isolated DNA molecule which comprises an expression system for the production of a calcium ion channel α_1 subunit protein which expression system comprises

a nucleotide sequence encoding a functional T-type, low voltage activated calcium channel α_1 subunit or the complement to said encoding nucleotide sequence, wherein said encoding nucleotide sequence comprises

(a) a nucleotide sequence encoding the amino acid sequence encoded by SEQ. ID. NO: 18; or

(b) the complement of a nucleotide sequence that hybridizes under conditions of medium hybridization stringency to the nucleotide sequence of (a).